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Viral Infections Among Patients With Hemophilia in the State of Georgia

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This analysis evaluated the extent to which infections with selected blood-borne viruses, specifically infection with hepatitis B virus, hepatitis C virus, and/or the human immunodeficiency virus (HIV), continue to contribute to the morbidity of persons with hemophilia. The Georgia Hemophilia Surveillance System collected information on 336 state residents with hemophilia A or B who were followed by a physician in 1994. Data abstracted from medical records included information on demographics, sources of hemophilia care, clinical characteristics, joint range of motion measurements, hospitalization, and results of laboratory testing for hepatitis B, hepatitis C, and the human immunodeficiency virus. Prevalence of infection with one or more of these viruses was determined, and relationships with disease severity, bleeding frequency, and amount of clotting factor prescribed were explored. No child under the age of ten was positive for the human immunodeficiency virus; hepatitis infection was also uncommon in this age group, in contrast to the very high frequency of such infections among older subjects. There was a strong association between HIV positive status and infection with one of the hepatitis viruses. The likelihood of all types of viral infection increased with frequency of bleeding and with amount of clotting factor received. Efforts to prevent transmission of lipid-enveloped viruses via clotting factor have been extremely effective. However, currently infected hemophilia patients will likely experience significant morbidity and mortality due to chronic liver disease and AIDS-related complications. Am. J. Hematol. 59:36–41, 1998.

Key words: hemophilia; Christmas disease; hepatitis viruses; HIV; epidemiology

INTRODUCTION

The history of hemophilia treatment is a varied one, marked by great accomplishments as well as tragic setbacks. Early attempts to control bleeding episodes involved techniques that were somewhat effective, including cautery, application of ice, and splinting, as well as more suspect methods such as ingestion of lead or strychnine or the injection of female hormones [1]. Premature death due to the disease remained a serious problem even into the first half of the twentieth century. With the transition from clinical to laboratory diagnosis of hemophilia in the 1940s, transfusion therapy was established as a primary treatment modality [1,2], with a significant improvement in effectiveness. Fresh frozen plasma was used for replacement of the deficient clotting factor during the next decade but retained the disadvantage of fluid overload and still required that the patient be treated in a hospital, physician's office, or emergency room. The discovery of cryoprecipitate and early factor concentrates in the 1960s and lyophilized concentrates in the 1970s revolutionized life for patients with hemophilia, allowing for treatment of bleeds at home and making elective surgery feasible for the first time [3]. In the 1980s and 1990s the focus has been on producing highly purified products, with fewer contaminants and greater specific activity. Advances in approaches to treatment brought with them great improvement in both longevity and quality of life

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for persons with hemophilia. There were dramatic decreases in time lost from work or school as well as in time spent in the hospital, and by 1980 most hemophilia patients could finally expect to achieve a normal life span [2,4,5].

These therapeutic advances, however, were associated with significant negative consequences as well. Serious complications resulting from the use of human clotting factor concentrates made from 20,000 or more donations per plasma pool became apparent soon after their introduction [6,7]. Foremost among these complications is the transmission of plasma-borne viruses, especially hepatitis B virus (HBV), hepatitis C virus (HCV), and the human immunodeficiency virus (HIV). Clinical hepatitis following infusion of multi-donor clotting factor concentrates began to be reported in the early 1970s [4,8,9]. Ultimately, the vast majority of hemophilia patients who received non-heat–treated concentrates were found to have antibody to hepatitis B (HBsAb), indicating exposure to the virus. Although only 5–10% of such patients became chronic carriers of hepatitis B, this group was put at a significantly increased risk of developing chronic liver disease or carcinoma of the liver. Users of multi-donor concentrates were also found to be at risk of liver disease due to an agent other then previously identified hepatitis viruses. Non-A, non-B hepatitis was a diagnosis of exclusion until the late 1980s when hepatitis C virus was characterized and an antibody test developed. Once reliable testing was available, it was discovered that virtually all hemophilia patients exposed to non-heat–treated factor were HCV positive [3,4,10]. The early course of hepatitis due to HCV is generally benign; however, at least 50% of patients later show evidence of chronic hepatitis, and 10–20% ultimately develop progression to chronic active hepatitis or cirrhosis [11,12].

The human immunodeficiency virus was introduced into the blood supply in the late 1970s [2,9,13], and persons with hemophilia were at extremely high risk of infection during the several years that followed. Incidence of HIV infection in this population peaked in the early 1980s; by 1982 over 50% of hemophilia patients in the United States had seroconverted [2,13]. The cumulative incidence of HIV infection varied with the amount of clotting factor received; estimates as high as 96% have been reported for patients who averaged over 50,000 units of factor VIII concentrate per year between 1978 and 1984 [13].

In 1993, the Centers for Disease Control and Prevention initiated hemophilia surveillance in six U.S. states, including Colorado, Georgia, Louisiana, New York, Massachusetts, and Oklahoma. One objective of this effort was to assess the impact of the disorder on patients with hemophilia by investigating treatment-related morbidity due to blood-borne viruses. This paper utilizes data from the Georgia site to evaluate the extent to which viral infections, specifically infection with HBV, HCV, and/or HIV, continue to contribute to the morbidity of persons with hemophilia.

METHODS

Since the initiation of hemophilia surveillance, personnel from the Georgia Hemophilia Surveillance System (GHSS) have been involved in an on-going effort to obtain information on all Georgia residents with hemophilia A (factor VIII deficiency) or B (factor IX deficiency). Identification of subjects has occurred primarily via collaboration with staff at the state's three hemophilia treatment centers as well as contact with hospitals and private physicians throughout the state. Information has also been gathered from sources such as factor concentrate distribution records and computerized Medicaid and vital records databases. Medical records and other data sources have been abstracted for information on demographics, sources of hemophilia care, clinical characteristics (bleeding frequency, type and amount of factor products used, signs and symptoms of hepatitis, etc.), laboratory test results, joint range of motion measurements, and hospitalizations. If information was available from several sources, a composite abstract was constructed for the calendar year, prior to data entry.

For calendar year 1994, 405 Georgia residents with hemophilia A or B have been identified by GHSS staff and entered into the surveillance database. For 69 of these subjects, however, there was no evidence of an encounter with the medical care system during that year and thus no medical record from which the relevant surveillance information could be abstracted. Therefore, these subjects have been designated as ''inactive'' for 1994 and were excluded from the present study population, leaving a total of 336 active hemophilia patients for analysis. Cases are considered definitive if there is a physician diagnosis of hemophilia A or B as well as laboratory confirmation of a factor VIII (hemophilia A) or factor IX (hemophilia B) activity level of 30% or less. Presumptive cases are those for which only one of these criteria can be documented. All 336 subjects in the current analysis have been diagnosed by a physician as having hemophilia A or B, and 324 (96%) also have a confirmed factor activity level of 30% or less.

Hepatitis information was taken from the laboratory section of medical and hospital records. Each person tested in 1994 was characterized as being either positive or negative for: Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and hepatitis C antibody. If no result could be found in the chart, it was assumed that the test had not been performed during that year. Determination of hepatitis B serostatus was based almost exclusively on the results of the core antibody test. One subject with no

TABLE I. Relationship Between Age and Seropositivity for Selected Viruses Among Hemophilia Patients*

	Age (years)								
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	All ages
% HIV+	0 (84)[a]	23.3 (86)	78.6 (56)	60.0 (45)	50.0 (26)	60.0 (10)	40.0 (5)	0 (2)	36 (314)
% HBV+	2.7 (37)	39.4 (33)	74.3 (35)	79.3 (29)	90.9 (11)	100 (4)	100 (1)	100 (2)	53 (152)
% HCV+	9.1 (77)	81.5 (54)	94.9 (39)	94.4 (36)	88.2 (17)	100 (5)	100 (3)	100 (2)	63 (233)

*HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a]Values in parentheses indicate the total number of persons in the designated age group for whom test results were available.

core antibody test result was classified as HBV positive based upon a positive surface antigen test. Data pertaining to infection with HIV were taken from physician notes as well as from reports of laboratory test results. Items of interest include: testing for HIV during the calendar year, seroconversion during the calendar year, and whether the subject had ever been reported as HIV seropositive.

Descriptive analysis of the data involved characterizing the study population by factor deficiency type, race, factor activity level, number of bleeds during the year, and number of units of factor prescribed during the year. Prevalences of infection with HBV, HCV, and HIV were calculated, overall as well as by decade of age. Associations between HIV infection and hepatitis were explored using prevalence odds ratios and corresponding *P*-values, comparing HIV positive and HIV negative subjects with regard to their likelihood of being HBV or HCV positive. Similar techniques were used to assess the relationship between factor activity level and infection with HIV as well as simultaneous infection with more than one virus. For each of the three types of viral infections, differences by serostatus in the average number of bleeds or average number of units of factor prescribed were evaluated using t-tests; this analysis was repeated after stratification by factor activity level. Average number of units of clotting factor prescribed was also calculated by number of concurrent viral infections (HIV, HBV, and/or HCV).

RESULTS

Of the 336 subjects in the study population, 279 (83%) were deficient in factor VIII and 57 (17%) were deficient in factor IX. Nearly two-thirds of the subjects were white and 30% were black; only 4% were from other racial backgrounds. (This racial distribution is quite similar to that of the general population of Georgia. Georgia's Office of Planning and Budget (OPB) estimates that 71% of the population was white, 26% black, and 3% other races in 1994.) Forty-five percent of subjects were considered to have severe disease (<1% factor activity level), 34% had moderate disease (1–5% factor activity level), and 18% had mild disease (6–30% factor activity level). For ten patients, the factor activity level was greater than 30% or was not documented. The median number of bleeds for the year was 11, with a range from zero to 208. The median number of units of factor prescribed was 31,440, with a range from zero to just under 970,000.

Prevalence of infection with HBV, HCV, and HIV, overall and by decade of age, is summarized in Table I. No child under the age of 10 was HIV positive; hepatitis B and hepatitis C infection were also uncommon in this age group, in contrast to the very high frequency of these infections among older subjects. As illustrated in Figures 1 and 2, infection with HIV was strongly predictive of concurrent infection with either HBV or HCV. Among the 149 patients tested for both viruses, the odds ratio for HBV infection, comparing HIV positive and HIV negative subjects, was 5.9 ($P = .000001$). Likewise, among the 226 patients tested for both viruses, the odds ratio for HCV infection, comparing HIV positive and HIV negative subjects, was 40.0 ($P = .000001$). This observation was driven largely by the low prevalence of HCV infection among subjects aged 0–9, all of whom were HIV negative. However, even among older subjects, the prevalence of HCV infection was consistently higher in those who were HIV positive. HIV status was also significantly related to baseline factor activity level, with more severely affected subjects (≤5% factor activity) more likely to be infected than those with milder disease (factor activity >5%) (odds ratio = 5.2, $P = 0.000073$). A similar association was seen between severity of hemophilia and the presence of more than one infection (odds ratio = 3.3, $P = 0.0014$).

As shown in Figure 3, there was a strong relationship between viral infection and frequency of bleeding. HIV positive subjects experienced an average of 25.4 bleeds during the year, compared with 14.3 among those who were HIV negative. An average of 23.3 bleeds during the year were reported by HBV positive subjects, compared with 14.5 among those who were HBV negative. HCV-infected subjects averaged 23.5 bleeds during the year,

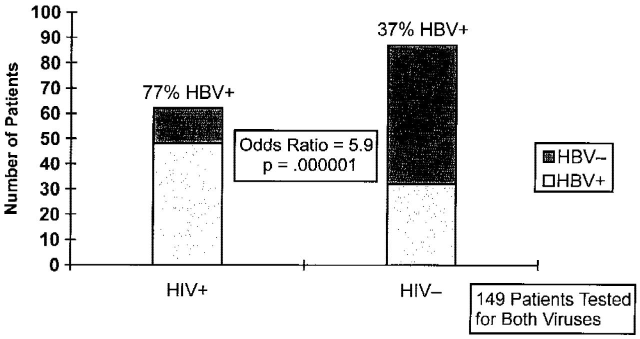

Fig. 1. HBV seropositivity by HIV status among patients with hemophilia.

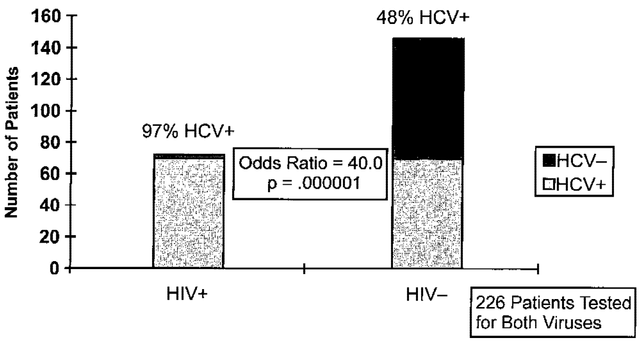

Fig. 2. HCV seropositivity by HIV status among patients with hemophilia.

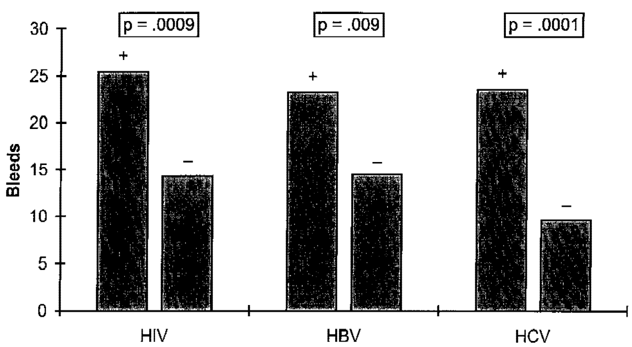

Fig. 3. Average number of bleeding episodes among hemophilia patients by viral status.

compared with 9.6 in the HCV negative group. A similar analysis, illustrated by Figure 4, indicated that HIV, HBV, and HCV positive subjects had been prescribed substantially more clotting factor during the year than had their virus-negative counterparts. Each of these differences was highly statistically significant. After stratification by factor activity level (<1%, 1–5%, >5%), it was still observed that virus-positive patients reported more bleeds and were prescribed more clotting factor than their uninfected counterparts. However, due to sample size limitations, many of these comparisons were no longer statistically significant. As shown in Table II,

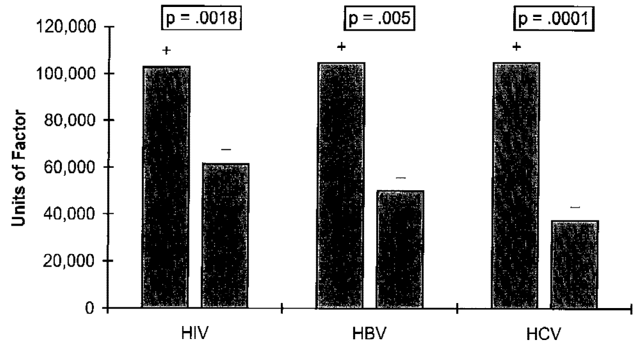

Fig. 4. Average number of units of clotting factor among hemophilia patients by viral status.

TABLE II. Number of Concurrent Viral Infections (HIV, HBV and/or HCV) and Amount of Clotting Factor Used in 1994*

Number of infections (n)[a]	Average number of units of clotting factor
0 (33)	27,248
1 (18)	75,499
2 (44)	96,391
3 (38)	118,184

*HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

[a]Number of subjects (includes only those patients who were tested for all three viruses).

there was a direct relationship between the number of concurrent infections (HIV, HBV, and/or HCV) and the average number of units of clotting factor used in 1994. This analysis was restricted to the 133 patients for whom test results were available for all three viruses.

DISCUSSION

A number of strategies have been implemented in order to reduce, and ultimately eliminate, the risk of virus transmission via blood and blood products. The simplest and least effective of these measures has been to discourage those at high risk of harboring infection from becoming blood donors. As appropriate tests became available, protocols for the screening of donated blood for viral contamination were established [7]. Screening of blood for hepatitis B surface antigen was first required in 1972, and an improved screening test was put into place by 1976. Screening of blood and plasma for HIV began in 1985, the year after HIV was identified. Prior to the specific characterization of the hepatitis C virus, blood donations were tested for alanine aminotransferase (ALT) and hepatitis B core antibody as surrogate testing for non-A, non-B hepatitis. Screening of whole blood for anti-HCV antibody was instituted in 1990. By this time, further precautionary measures of particular relevance to the hemophilia population had already been imple-

mented, in the form of viral inactivation techniques for treating human clotting factor concentrates. In an effort to prevent transmission of hepatitis, U.S. manufacturers began exploring the utility of heat treatment of concentrates in the late 1970s [7]. Heating in solution was originally associated with unacceptably low yields, leading to the development of dry heat techniques. During the early to mid 1980s there was a great deal of experimentation and refinement, with many variations in temperature, moisture, and duration of heating of concentrates. Throughout this process, hepatitis viruses proved to be more resistant to inactivation than HIV. In 1985 a new technique, solvent-detergent viral inactivation, was licensed for the treatment of factor concentrates. This method quickly gained popularity, as it was shown to be quite effective against lipid-enveloped viruses such as HBV, HCV, and HIV [7,14–16]. Reduction in risk of viral transmission was also achieved by advances in factor purification techniques [1]. Although inadequate for complete elimination of contaminants, immunoaffinity chromatography using monoclonal antibodies to specific clotting factors removes a substantial amount of virus from clotting factor concentrates [7]. The development of a vaccine against hepatitis B was another notable event in the effort to prevent viral infections among patients with hemophilia, as was the production of recombinant factor.

Analysis of data from the GHSS demonstrates the profound impact that risk-reduction techniques, particularly lipid-envelope virus inactivation, have had on the risk of acquiring a morbid blood-borne virus from clotting factor concentrate. Children in Georgia who were born after 1985 have no evidence of HIV infection and a substantially reduced frequency of HBV and HCV infection compared to older individuals. This decline in risk has been observed by others as well [17–19]. As illustrated previously for HIV [13], the risk of infection with each of these viruses is related directly to the severity of the hemophilia. Individuals with more severe disease bleed more frequently and require more clotting factor, thus increasing their risk of blood-borne infections. Even among patients with milder disease, the likelihood of infection increases with bleeding frequency and amount of factor used, indicating that these are the key risk factors of interest.

Although the occurrence of new infections with HBV, HCV, and HIV has decreased substantially in recent years, these viruses continue to be of significant concern to persons with hemophilia and their caregivers. The impact of HIV infection has been devastating, and, despite recent advances in treatment, it is likely to be felt for some time into the future. Estimates from our surveillance data indicate that nearly 40% of the hemophilia population in Georgia was HIV positive in 1994. Data from Pennsylvania illustrate the dramatic effect of HIV on mortality among persons with hemophilia [11]. Among a cohort of patients receiving state-supported comprehensive care who were followed from 1976 to 1991, there were no deaths due to AIDS during the first five years of the study. For each of the next two five-year periods, the proportions of deaths due to AIDS rose to 20% and 64.5%, respectively. During the decade of the 1980s, median age at death for persons with hemophilia decreased by 17 years as a result of AIDS-related complications [20].

Another important problem is that of multiple infections, especially the combination of hepatitis C and HIV. As expected, given their similar routes of transmission, such coinfection is common among persons with hemophilia [21–23]. This is illustrated by our surveillance data, which indicated that among HIV infected subjects, 77% were HBV positive and 97% were HCV positive. Hepatitis C virus is now the predominant cause of chronic liver disease among hemophilia patients [21,24,25], and there is substantial evidence that simultaneous infection with HIV accelerates the progression of HCV-related liver disease. Case reports of rapidly progressive liver disease among HIV positive patients with non-A, non-B hepatitis were published nearly a decade ago [26]. This observation was later confirmed in cohort studies describing the natural history of hepatitis C infection among HIV positive and HIV negative patients [3,12,27]. Telfer et al. [3] reported that HIV positive subjects with hepatitis C were 21 times as likely as their HIV negative counterparts to decompensate. More recent research has focused on potential mechanisms for the interaction of HCV and HIV. Several studies have suggested there may be enhanced HCV replication among HIV positive subjects, presumably due to their immune suppression [22,28]. The probable multifactorial nature of liver failure among persons with hemophilia has been explored by Eyster et al. [12], who found lymphocytopenia among HCV positive subjects prior to the onset of HIV infection. This observation prompted them to speculate that clotting factor concentrates, HCV infection, or chronic liver disease itself might be responsible for immune suppression, which in turn promotes HCV replication and accelerates development of liver failure. HIV infection could further enhance this process. Whatever the mechanism, HCV-related chronic liver disease, especially among those with concurrent HIV infection, is likely to remain a significant problem in the hemophilia population for many years to come.

Transmission of viruses via blood products has been a significant source of morbidity for persons with hemophilia. Fortunately, a number of effective strategies, including donor screening and viral inactivation procedures, have been implemented in order to prevent such transmission in the future. The most recent innovation in hemophilia treatment has been the introduction of recombinant factor therapy, which holds great promise for

safety as well as efficacy. Although expensive, it should provide a bridge to gene therapy, which has the potential to normalize the lives of most persons with hemophilia and eliminate the complications experienced by their predecessors.

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